Published in final edited form as:
J Allergy Clin Immunol. 2009 February ; 123(2 Suppl 1): S24. doi:10.1016/j.jaci.2008.12.106.

Sesame Allergy: Role of Specific IgE and Skin Prick Testing in Predicting Food Challenge Results

Perdita Permaul, MD[a,b], **Lisa M. Stutius, MD**[a,b], **William J. Sheehan, MD**[a,b], **Pitud Rangsithienchai, MD, MA**[a,c], **Jolan E. Walter, MD, PhD**[a,b], **Frank J. Twarog, MD, PhD**[a,b], **Michael C. Young, MD**[a,b], **Jordan E. Scott, MD**[a,b], **Lynda C. Schneider, MD**[a,b], and **Wanda Phipatanakul, MD, MS**[a,b]

[a] Department of Medicine, Division of Allergy and Immunology, Children's Hospital Boston, Boston, Massachusetts

[b] Harvard Medical School, Boston, Massachusetts

[c] McGraw Medical Center, Northwestern University, Evanston Program, Evanston, Illinois

INTRODUCTION

Sesame seed is an emerging food allergen in the U.S. pediatric population as it becomes more common in the American diet. A recent systematic review of seed allergies described a prevalence of < 1% for sesame allergy as defined by a positive food challenge.1 It has been reported that most patients have sesame allergy before the age of 2 and about 20% of children with clinical allergy eventually develop tolerance.2 Another study described 9 of 30 children (30%) developing tolerance at an average age of 2.8 years.3 Dalal et al. reported anaphylaxis as the presenting symptom in 30% of children with sesame allergy, all occurring in patients less than 1 year of age.4 This is of significant clinical concern in children who are too young to describe their symptoms.

Clinical diagnostic tests such as food-specific IgE levels and skin prick test (SPT) results may aid in deciding who will tolerate a food challenge compared to those who are likely to react.5 Diagnostic decision points for food-specific IgE antibodies have been published for common food allergens such as egg, milk, peanut and fish.6, 7 However, there is conflicting data regarding the diagnostic value of sesame-specific IgE and SPT and currently there are no established thresholds that predict clinical reactivity. Zavalkoff et al. were unable to establish a sesame-specific IgE threshold with a 95% positive predictive value.8 In a paper published by Maloney et al., a fitted predicted probability curve of clinical reactivity to sesame in relation to sesame-specific IgE did not show a 90% or 95% predicted probability of a reaction.9 Lastly, Ho et al. identified a sesame SPT wheal diameter ≥ 8 mm as being predictive of a positive food challenge with > 95% accuracy.10

Corresponding author: Perdita Permaul, MD, Children's Hospital Boston, Division of Allergy and Immunology, Children's Hospital Boston, 300 Longwood Avenue, Fegan Building 6th Floor, Boston, MA 02115, Telephone: 917-517-8333, Fax: 617-730-0310, Perdita.Permaul@mssm.edu.

Presented at the American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting March 13-17, 2009.

Conflict of Interest: There are no conflicts of interest to note for each of the authors. There are no other funding sources to note except for what is noted above. There are no institutional or corporate affiliations to note for each of the authors.

METHODS

The objective of this study was to examine the correlation of sesame-specific IgE and SPT results with the outcome of oral sesame challenges in children suspected of having a sesame allergy. Children were suspected of having a sesame allergy for a variety of reasons including a positive sesame ImmunoCAP and/or SPT, worsening eczema with sesame ingestion, clinical reaction to sesame such as urticaria, angioedema, respiratory distress, or gastrointestinal symptoms including emesis and diarrhea. We conducted a retrospective chart review of all children, age 2 to 12 years, who received a serum sesame-specific IgE level, SPT, and oral food challenge from January 2004 to August 2008 at Children's Hospital Boston and several affiliated allergy clinics.

Oral food challenge was used as the gold standard by which performance characteristics (sensitivity, specificity, positive and negative predictive values) of sesame-specific IgE measurements and SPT wheal size were calculated. Receiver operator characteristic curve (ROC) analysis was utilized to determine a threshold that would differentiate children with true sesame allergy from those who are tolerant. The relationship between sensitization status and outcome measure was analyzed using logistic regression. Fitted predicted probability curves were plotted using the results from logistic regression.

Serum samples were analyzed for sesame-specific IgE using an ImmunoCAP fluorescence enzyme immunoassay (Phadia AB, Portage, MI). The detection limit of the assay was 0.35 kU/L. A positive ImmunoCAP test was defined as ≥ 0.35 kU/L.

Skin prick tests were performed in a standard fashion using the Multi-Test II device from Alk-Abello (Round Rock, TX) and commercially prepared extract from Greer Laboratories (Lenoir, NC). Negative controls with saline and positive controls with histamine were performed concurrently. The mean of the longest diameter and orthogonal diameter were measured in millimeters at 15 minutes. A positive SPT was defined as a wheal diameter ≥ 3 mm larger than the negative control.

Oral food challenges were performed as graded open challenges according to recommendations of the American Academy of Asthma, Allergy and Immunology and the American College of Allergy, Asthma and Immunology.11 Sesame seeds were used for challenge. A standard graded open food challenge consisted of increasing increments every 15 minutes of 100 mg, 500 mg, 1 g, 2 g, 4 g, and 4 g of sesame seeds. Children less than 3 years of age were given increasing increments every 15 minutes of 500 mg, 1 g, 2 g, and 4 g. Symptoms that warranted cessation of a food challenge included urticaria, rhinitis, wheezing, throat itchiness, angioedema, worsening of eczema, emesis, and refusal to eat. Food challenges were conducted in cases of questionable clinical history or a negative sesame-specific IgE and/or negative SPT despite a convincing history.

RESULTS

Thirty-three oral sesame challenges were performed in 33 children. Sixty-one percent of patients had atopic dermatitis, 48% asthma, 45% history of anaphylaxis to another food, and 24% had a first-degree relative with food allergy. Of the 33 oral sesame challenges performed, 21% (N=7) were assessed as positive and 79% (N=26) as negative. Of the symptoms provoked by the oral food challenge, 71% were cutaneous, 43% gastrointestinal, 29% involved mucous membranes, 29% involved the lower respiratory tract, and 29% manifested as anaphylaxis.

Of the 33 patients suspected of having a sesame allergy, 7 had never ingested sesame but had positive testing. Of these 7 patients, 3 failed the oral challenge (see Table I). In addition,

9 of the 33 patients were tested via sesame-specific IgE level and/or SPT to confirm a clinical reaction to sesame while the remaining patients were screened due to the presence of other food allergies such as peanut and tree nuts. The clinical allergic reactions in these 9 patients included urticaria, lip swelling, possible anaphylaxis, and worsening eczema with ingestion. Interestingly, these 9 patients passed the oral challenge.

Eighteen of 26 (69%) sesame tolerant children had a positive ImmunoCAP test. Eleven (42%) sesame tolerant children had a positive SPT. Two of 7 (29%) sesame allergic children had a negative SPT result, one of which also had a negative ImmunoCAP test (see Table 1 – patient 3). This patient previously tolerated sesame but began restricting it from the diet based on positive testing performed in the past as part of screening for peanut and tree nut allergies.

With respect to sesame-specific IgE, sensitivity was highest at a lower cutoff value, whereas specificity increased at higher values (see Table II). A positive ImmunoCAP test demonstrated 71% sensitivity, 31% specificity, 22% positive predictive value (PPV), and 80% negative predictive value (NPV). The negative predictive value increased up to a threshold of 1 kU_A/L. A sesame-specific IgE level ≥ 7 kU_A/L demonstrated specificity > 90%. ROC curve analysis for sesame-specific IgE revealed an area under the curve (AUC) of 0.56 (see Figure 1). For varying SPT cut-offs, sensitivity was highest at a lower cutoff value and specificity increased at higher values (see Table III). A positive SPT demonstrated 71% sensitivity, 58% specificity, 31% PPV, and 88% NPV. A SPT wheal size ≥ 6 mm demonstrated specificity > 90%. ROC curve analysis for SPT wheal size revealed an AUC of 0.67 (see Figure 1).

DISCUSSION

The prevalence of sesame allergy varies geographically with increasing prevalence in regions with greatest exposure. Sesame is a common food allergen in countries such as Israel, Japan and Europe where it is regularly consumed in the diet. It is becoming more common in the American diet due to immigration and globalization and as a result has become an emerging cause of severe allergy in the U.S.

We know that direct exposure to sesame causes sensitization but it has been hypothesized that there may also be cross-reactivity between peanut and sesame allergies. Ho et al. reported a high rate of sesame sensitization (27.5%) in persistent peanut allergic children despite complete restriction of sesame from the diet, suggesting antigenic cross-reactivity.12 A proposed mechanism cited for this cross-reactivity includes homology among the seed storage proteins and oleosins.2 Major allergenic seed storage proteins described for sesame seed are Ses i 1, Ses i 2, and Ses i 3.13 Oleosins (Ses i 4 and Ses i 5) are oil body proteins and have recently been described as major allergens in sesame, hazelnuts, and peanuts.2, 13 Given this concern for cross-reactivity between peanut and sesame, many allergists are screening peanut allergic children for sesame allergy by specific IgE level and/or SPT. As a result, there are more sesame sensitized children than ever before. However, it remains unclear whether sesame sensitization implies clinical reactivity.

The aim of this study was to elucidate the predictive relationship of sesame-specific IgE and SPT results to sesame challenge outcomes. While we did not find a diagnostic decision point for sesame SPT, there was a trend for more predictability with SPT compared to sesame-specific IgE (see Figures 2A and 2B). The SPT AUC was higher than for sesame-specific IgE although not significant. It is noteworthy that 69% of children passing the sesame oral food challenge exhibited a positive ImmunoCAP test; 39% of these children had a level > 2.0 kU_A/L.

The performance characteristics of both diagnostic tests at several decision points revealed poor sensitivities and positive predictive values, indicating a low likelihood of disease in those with levels greater than the decision points. Both ImmunoCAP testing and SPT revealed high specificities at a cut-off ≥ 7 kU_A/L and ≥ 6 mm, respectively, confirming that the tests perform well in those without sesame allergy. Notably, 29% of sesame allergic patients had a sesame-specific IgE < 0.35 kU_A/L. This is in contrast to the findings of Zavalkoff et al. who reported a cut-off < 0.35 kU_A/L as being useful in excluding a diagnosis of sesame allergy.8 A SPT wheal size of < 3 mm approached an NPV of 90%. Therefore, patients with a negative SPT are likely to have no clinical reactivity with the ingestion of sesame.

A potential limitation of this study is that the majority of food challenges were conducted in patients found to be positive on a sesame screen and in those with a negative ImmunoCAP and/or SPT result despite a convincing history which could account for the low rate of positive food challenges. A large number of these patients (N=24) were suspected of having sesame allergy based on a positive sesame ImmunoCAP test and/or SPT performed as a screen in those with peanut and tree nut allergies. However, this subset of patients can help elucidate whether sesame sensitization predicts clinical reactivity based on food challenge outcome. It is quite interesting that all 7 failed food challenges were patients screened for sesame allergy as a result of having peanut and tree nut allergies; 4 had previously tolerated sesame but asked to restrict sesame from their diet based on positive results. The remaining 9 patients who did have a prior clinical reaction to sesame passed the food challenge.

Another limitation of this study, as well as others,8› 9 is that sesame allergy was determined by history rather than by the gold standard food challenge which could introduce recall and reporting bias. Given that this retrospective study was based on a pediatric population, performing food challenges as a diagnostic measure could be considered impractical and unethical. Further, Ho et al. utilized a 20 g total sesame dose for food challenges while our maximal sesame dose was 11.6 g in those older than 3 years.10 There may be a higher sesame ingestion threshold for which clinical reactions occur but practically it would be difficult to have children ingest such large quantities of sesame.

Although our study is limited by a small sample of cases, there is an inclination for predicting the outcome of a sesame food challenge with SPT based on our results. Until larger studies are performed, clinicians should consider challenging patients to sesame regardless of sesame-specific IgE or SPT values, unless there is a compelling history of an allergic reaction to sesame. In cases where sesame is clearly tolerated, neither ImmunoCAP testing or a SPT should be obtained given the potential for false positives and unnecessary food restriction. It is also uncertain whether restricting foods from the diet could lead to a decrease in tolerance to that food as is exemplified by patient 3 in Table I. Moreover, a negative ImmunoCAP test should be interpreted in the context of history and SPT.

To our knowledge, this study represents the largest number of sesame food challenges performed to evaluate the diagnostic value of both sesame-specific IgE and SPT. Cohen et al. found no relationship between sesame-specific IgE, SPT, and oral food challenge outcome in 22 children.2 There are studies with larger numbers of oral challenges examining either sesame-specific IgE or SPT, however. For instance, Ho et al. examined the diagnostic accuracy of sesame SPT in 60 children with sesame allergy and identified a wheal diameter ≥ 8 mm as being predictive of a positive food challenge with > 95% accuracy.10

Our results confirm that a positive sesame-specific ImmunoCAP test and positive sesame SPT are not good predictors of true sesame allergy as determined by the gold standard test

of an oral sesame challenge. We were unable to establish a threshold with a 95% positive predictive value for both sesame-specific IgE and SPT. ROC curve analysis revealed poor AUC values for both diagnostic testing modalities. Our data add to previous results from other studies and further confirms variation among studies. At this time, caution should be taken in applying these results to patient populations.

Acknowledgments

Declaration of all sources of funding: Dr. Permaul is supported by an NIH NRSA grant (T32-AI-007512). Dr. Phipatanakul is supported by an NIH K-23 grant (AI-054972) and an NIH R-01 grant (AI-073964).

References

1. Zuidmeer L, Goldhahn K, Rona RJ, et al. The prevalence of plant food allergies: a systematic review. J Allergy Clin Immunol. 2008; 121(5):1210–8. e4. [PubMed: 18378288]
2. Cohen A, Goldberg M, Levy B, Leshno M, Katz Y. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. Pediatr Allergy Immunol. 2007; 18(3):217–23. [PubMed: 17346302]
3. Aaronov D, Tasher D, Levine A, Somekh E, Serour F, Dalal I. Natural history of food allergy in infants and children in Israel. Ann Allergy Asthma Immunol. 2008; 101(6):637–40. [PubMed: 19119709]
4. Dalal I, Binson I, Levine A, Somekh E, Ballin A, Reifen R. The pattern of sesame sensitivity among infants and children. Pediatr Allergy Immunol. 2003; 14(4):312–6. [PubMed: 12911511]
5. Cox L, Williams B, Sicherer S, et al. Pearls and pitfalls of allergy diagnostic testing: report from the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Specific IgE Test Task Force. Ann Allergy Asthma Immunol. 2008; 101(6):580–92. [PubMed: 19119701]
6. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997; 100(4):444–51. [PubMed: 9338535]
7. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001; 107(5):891–6. [PubMed: 11344358]
8. Zavalkoff S, Kagan R, Joseph L, St-Pierre Y, Clarke A. The value of sesame-specific IgE levels in predicting sesame allergy. J Allergy Clin Immunol. 2008; 121(6):1508–10. [PubMed: 18539199]
9. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008; 122(1):145–51. [PubMed: 18502490]
10. Ho MH, Heine RG, Wong W, Hill DJ. Diagnostic accuracy of skin prick testing in children with tree nut allergy. J Allergy Clin Immunol. 2006; 117(6):1506–8. [PubMed: 16751023]
11. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008; 100(3 Suppl 3):S1–148.
12. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. J Allergy Clin Immunol. 2008; 121(3):731–6. [PubMed: 18234313]
13. Leduc V, Moneret-Vautrin DA, Tzen JT, Morisset M, Guerin L, Kanny G. Identification of oleosins as major allergens in sesame seed allergic patients. Allergy. 2006; 61(3):349–56. [PubMed: 16436145]

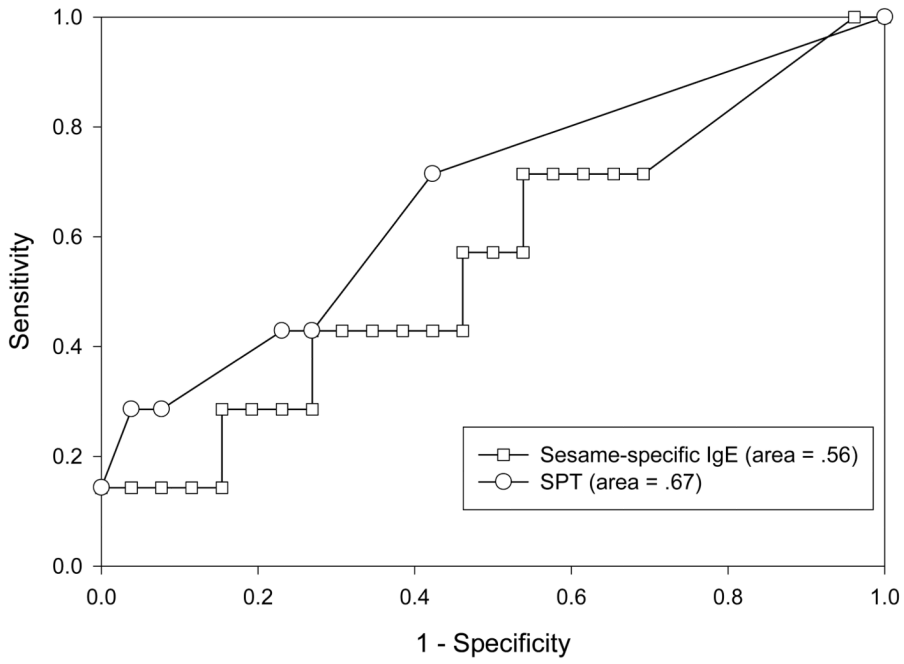

Figure 1.

Comparison of ROC curves for sesame-specific IgE and SPT and its area under the curve. These curves represent the probability of failing oral sesame challenge at a given value for sesame-specific IgE and SPT, N=33 oral sesame challenges.

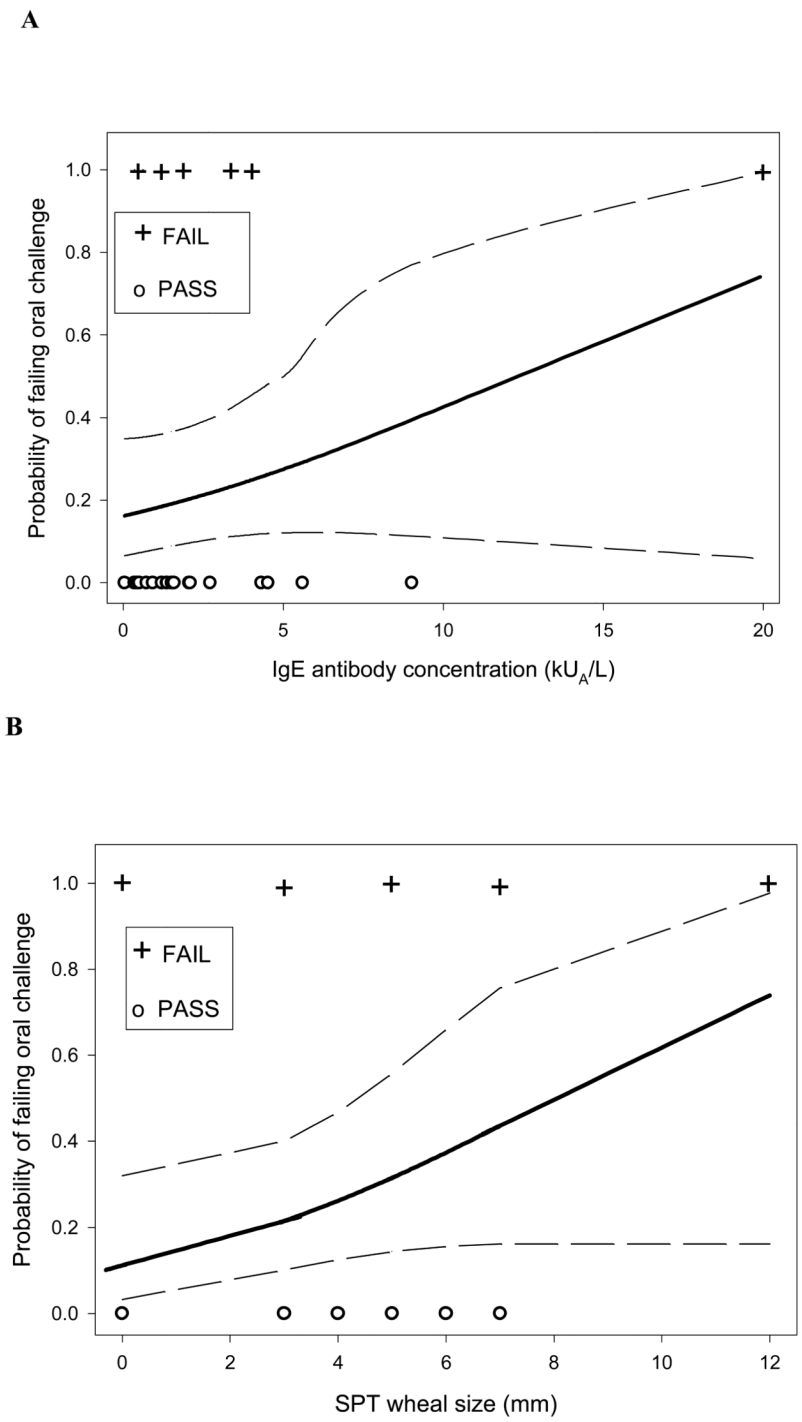

Figure 2.

(A) Estimated probability curve for failing oral sesame challenge at a given sesame-specific IgE antibody level derived from logistic regression, N=33 oral sesame challenges. Dashed lines indicate 95% prediction limits. (B) Estimated probability curve for failing oral sesame challenge at a given SPT wheal size derived from logistic regression, N=33 oral sesame challenges. Dashed lines indicate 95% prediction limits. **Note: There are multiple overlapping open circles depicted in** Figure 1 and Figure 2.

TABLE I

Failed sesame food challenge data, N=7. *SPT*, skin prick test; *PN*, peanut; *TN*, tree nut; *pos*, positive; *prev*, previously; *IVF*, intravenous fluids.

Patient	ImmunoCAP result (kU_A/L)	SPT wheal (mm)	Reason for challenge	Clinical reaction to challenge	Amount ingested prior to reaction	Medication given
1	0.61	5	never ingested, pos testing, PN and TN allergic	hives on arm	100 mg	diphenhydramine
2	1.85	0	never ingested, pos testing, PN and TN allergic	emesis	7 g	none
3	< 0.35	0	prev ingested, pos SPT in past, PN and TN allergic	cough, itchiness of skin	9 g	diphenhydramine
4	< 0.35	3	prev ingested, pos testing, PN and TN allergic	refusal to eat	1.5 g	none
5	1.17	7	never ingested, pos testing, PN and TN allergic	multiple hives50 minutes after completion	11.6 g	none
6	3.33	3	prev ingested, pos testing, PN and TN allergic	rhinitis, throat itchiness, emesis, hives, hypotension	100 mg	epinephrine, diphenhydramine, ranitidine, methyprednisolone, IVF
7	19.9	12	prev ingested pos testing, PN allergic	hives, wheezing, emesis	500 mg	epinephrine, diphenhydramine

J Allergy Clin Immunol. Author manuscript; available in PMC 2011 July 7.

TABLE II

Performance characteristics of sesame ImmunoCAP testing at various cutoff points

Cutoff (kU_A/L)	# (%) at or exceeding cutoff	# (%) children failing challenge and exceeding cutoff	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
< 0.35	33 (100%)	7 (100%)	100	0	21.1	---
≥ 0.35	23 (70%)	5 (71%)	71.4	30.8	21.7	80.0
≥ 0.7	18 (55%)	4 (57%)	57.1	46.2	22.2	80.0
≥ 1.0	16 (21%)	4 (57%)	57.1	53.8	25.0	82.4
≥ 1.5	12 (36%)	3 (43%)	42.9	65.4	25.0	81.0
≥ 3.0	6 (18%)	2 (29%)	28.6	84.6	33.3	81.5
≥ 3.5	5 (15%)	1 (14%)	14.3	84.6	20.0	78.6
≥ 7.0	2 (6%)	1 (14%)	14.3	96.2	50.0	80.6
≥ 17.5	1 (3%)	1 (14%)	14.3	100	100	81.8

TABLE III

Performance characteristics of sesame skin prick testing at various cutoff points

Cutoff wheal (mm)	# (%) at or exceeding cutoff	# (%) children failing challenge and exceeding cutoff	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
< 3	33 (100%)	7 (100%)	100	0	21.1	
≥ 3	16 (48%)	5 (71%)	71.4	57.7	31.3	88.2
≥ 4	10 (30%)	3 (43%)	42.9	73.1	30.0	82.6
≥ 5	9 (27%)	3 (43%)	42.9	76.9	33.3	83.3
≥ 6	4 (12%)	2 (29%)	28.6	92.3	50.0	82.8
≥ 7	3 (9%)	2 (29%)	28.6	96.2	66.7	83.3
≥ 12	1 (3%)	1 (14%)	14.3	100	100	81.3